ORGANIC LETTERS

2000
Vol. 2, No. 19
3003−3006

Catalysis by Amino Acid-Derived Tetracoordinate Complexes: Enantioselective Addition of Dialkylzincs to Aliphatic and Aromatic Aldehydes

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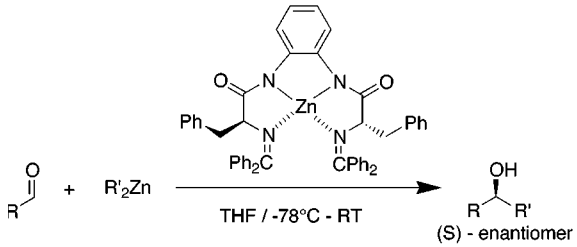
Received July 10, 2000

ABSTRACT



Me_2Zn and Et_2Zn added to aromatic and aliphatic aldehydes in the presence of 3 mol % of 2. (*S*)-1-Phenylethanol (91% ee) and (*S*)-1-phenylpropanol (86% ee) were synthesized from benzaldehyde and (*S*)-1-furan-2-yl-1-propanol (86% ee) from 2-furaldehyde. Nonanal and 3-phenylpropanal provided (*S*)-3-undecanol (96% ee) and (*S*)-1-phenyl-3-pentanol (94% ee). A solid-phase variant was effective with reduced ee's (e.g., 86% ee → 79% ee) for (*S*)-1-phenylpropanol.

Long since the early pioneering work of McKenzie,[1] asymmetric synthesis has become one of the cornerstones of organic synthesis. While McKenzie used a chiral auxiliary (menthol) for his work, the ideal or aspirational enantioselective reaction would use a cheap, renewable source of chirality[2] and would require only catalytic amounts (e.g., multiplication of chirality).[3] The addition of organozinc reagents[4] to aldehydes in the presence of catalytic amounts of chiral ligands is among the most successful catalytic reactions of this type.[5] Almost all the work with organozinc reagents has utilized chiral ligands possessing a β-amino alcohol moiety, which can bind zinc in a bidentate[6] or occasionally a tridentate manner.[7] After a search of the literature, we could find no examples of tetradentate ligands used in the addition of organozinc reagents to aldehydes. As part of our efforts to develop a "universal ligand", we were pleasantly surprised to find that a tetracoordinate zinc complex, formed from the amino acid-derived ligand system described previously,[8] worked quite well as a catalyst for the addition of alkylzincs to both aromatic and aliphatic aldehydes.

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(2) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis with Transition Metal Compounds, Vol II*; VCH: Weinheim, 1993.

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10.1021/ol0063151 CCC: $19.00 © 2000 American Chemical Society
Published on Web 08/19/2000

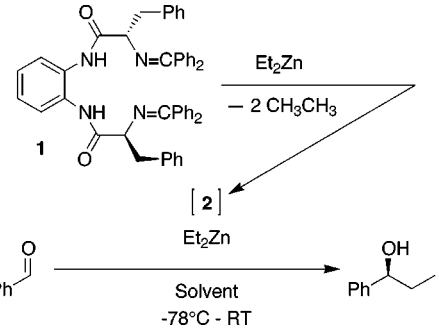
The reaction of Et_2Zn with ArCHO and RCHO in the presence of chiral ligand **1** was evaluated.[9] For these studies (Table 1) the reactive Zn^{II} complex **2** was formed in situ from Et_2Zn and ligand **1**. NMR studies showed that the zinc complex formed readily in d_8-THF or d_8-toluene. In THF one molecule of solvent appeared to coordinate axially to allow the zinc metal to adopt a square pyramidal geometry. The complex was stable in a dry, oxygen-free atmosphere. Complex formation was found to be complete after an hour at reflux. Once formed, the reaction mixture was cooled to −78 °C and the aldehyde was added in a single portion. Using a syringe pump, an equimolar amount of Et_2Zn in THF was added and the reaction continued for 16 h at rt. Analysis of the product mixture was performed by capillary GC.

The C_2-symmetric Zn^{II}-L-Phe-L-Phe complex **2** catalyzed the quantitative addition of Et_2Zn to PhCHO when 3−5 mol % of catalyst was used. THF was found to be the best solvent for the additions, but was not necessary for complex formation. With 1 mol % of catalyst the reaction proceeded but was incomplete after 16 h (rxn 1). EtZnI was not effective as an alkyl donor. Only one ethyl group was transferred from Et_2Zn at an appreciable rate. The second ethyl group was transferred, but much more slowly. In every case the major isomer was the *S*-enantiomer, [(*S*)-(−)-1-phenyl-1-propanol] in 82−86% ee.

It is noteworthy that, contrary to reports of studies performed with bidentate "Soai-type" catalysts, the polar solvent THF enhanced the enantioselectivity of Et_2Zn additions (Table 1). When toluene was used (rxn 3), the reactions went to completion, but the ee's dropped to 6%. Using a 2:1 mixture of toluene and THF decreased the ee's to 63% (rxn 4).

Given these results, several aldehydes were screened using 3 mol % of the Zn^{II}-L-Phe-L-Phe complex **2** (Table 2). A slight increase in enantioselectivity was observed when dimethylzinc was substituted for diethylzinc in the addition to benzaldehyde (rxn 5 vs rxn 2). 2-Furaldehyde gave ee's similar to those seen with benzaldehyde (rxn 6). Aliphatic aldehydes provided excellent ee's with this catalyst. Addition to 3-phenylpropanal (rxn 7) yielded pure (*S*)-(+)-1-phenylpentan-3-ol (94% ee), following chromatography and sublimation. The optical rotation of the sublimed alcohol was +23.6° (c = 1.56; $CHCl_3$). Similarly, addition to nonanal (rxn 8) provided (*S*)-(+)-3-undecanol (96% ee) after chromatography and vacuum distillation. The optical rotation of the distilled alcohol was +7.48° (c = 0.91; ethanol).[10] Both

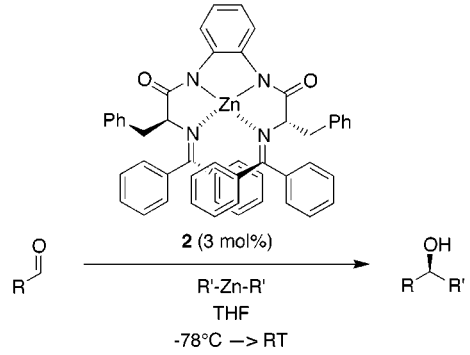
Table 1. Solvent Studies



rxn	catalyst (mol %)	solvent	chemical yield [a]	enantiomeric excess [b]
1	1	THF	(61%)	82%
2	3	THF	85% (99%)	86%
3	3	$PhCH_3$	(99%)	6.3%
4	3	$PhCH_3$ / THF (2:1)	(96%)	63%

[a] Isolated yields (tields in parentheses based on GC peak areas). [b] Determined by chiral GC: (*S*)-1-phenyl-propanol, Chiraldex β-PH (100 °C isotherm).

Table 2. Aromatic versus Aliphatic Substrates



rxn	R	R'	chemical yield [a]	enantiomeric excess [b]
5		CH_3-	80% (92%)	91%
6		CH_3CH_2-	30% (92%)	86%
7	$PhCH_2CH_2$-	CH_3CH_2-	27%[c] (81%)	94%[c]
8	$CH_3(CH_2)_7$-	CH_3CH_2-	51%[d] (99%)	96%[d]

[a] Purified yields (yields in parentheses based on GC peak areas). [b] Determined by chiral GC: 1-phenylpropan-1-ol, Chiraldex β-PH (100 °C isotherm); 1-furylpropan-1-ol, Chiraldex γ-TA (60 °C isotherm); (*R*)-(−)-Mosher's ester of 1-phenylpentan-3-ol and 3-undecanol, Chiraldex β-TA (140 °C isotherm). [c] Purified by flash, followed by sublimation. Observed $[\alpha]_D$ = + 23.6°; literature $[\alpha]_D$ = +23.8° (refs 10a and 10b). [d] Product purified by flash, followed by distillation. Observed $[\alpha]_D$ = + 7.48°; literature $[\alpha]_D$ = + 7.79° (ref 10c).

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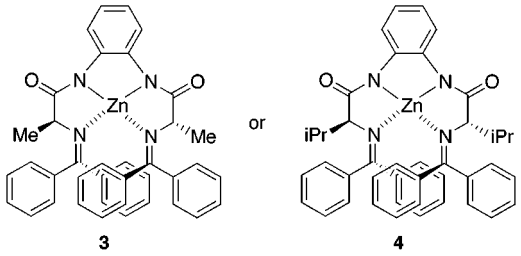
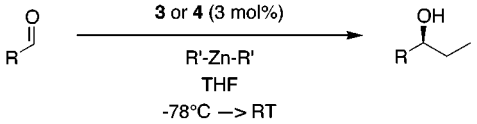
(9) Ligand **2** (219 mg, 0.3 mmol, 3 mol %) was azeotropically dried with $PhCH_3$ and then dissolved in 3 mL of THF. A 0.5 M solution of Et_2Zn in THF (0.64 mL, 0.32 mmol, 3.2 mol %) was added to **2** and heated to reflux for 1 h. After Zn insertion was complete, the reaction mixture was cooled to −78 °C and $PhCH_2CH_2CHO$ (1.34 g, 10.0 mmol) was added in a single portion. More 0.5 M Et_2Zn solution in THF (26 mL, 13.0 mmol, 1.3 equiv) was then added dropwise, and the mixture was allowed to warm slowly to rt. After 16 h the reaction was quenched with 1 M HCl and worked up in the usual manner to provide (*S*)-1-phenyl-3-pentanol. A detailed protocol may be found in the Supporting Information.

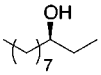
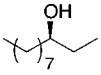
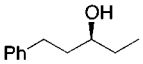
of these reactions were run on a 1-g scale, and the enantiomeric purity of the each alcohol was confirmed by formation of the corresponding Mosher esters (^{1}H NMR and chiral GC). Despite the higher enantioselectivities observed with the aliphatic aldehydes, the reactions were complicated by significant formation (~50% of the reaction mixture) of the corresponding aldol products.

Further studies with the L-Ala-L-Ala **3** and L-Val-L-Val **4** complexes have been performed (Table 3). As expected, the

Table 3. Enantioselectivity Depends on Steric Bulk of Amino Acid Residue





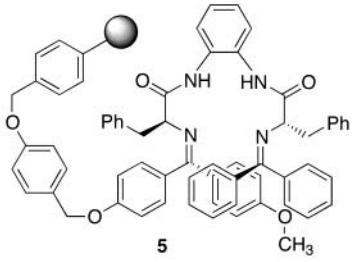
rxn	catalyst	substrate	product	chemical yield [a]	enantiomeric excess [b]
9	**3**	PhCHO		(86%)	19%
10	**3**	$CH_3(CH_2)_7CHO$		(70%)	27%
11	**4**	PhCHO		(99%)	91%
12	**4**	$CH_3(CH_2)_7CHO$		10%[c] (78%)	89%
13	**4**	$Ph(CH_2)_2CHO$		12%[c] (50%)	92%

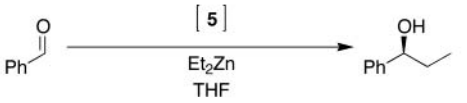
[a] Isolated yields (yields in parentheses based on GC peak areas). [b] Determined by chiral GC: 1-phenylpropan-1-ol, Chiraldex β-PH (100 °C isotherm); (*R*)−(−)-Mosher's ester of 1-phenylpentan-3-ol and 3-undecanol, Chiraldex β-TA (140 °C isotherm). [c] Products were purified by flash chromatography, follwed by sublimation (1-phenylpentan-3-ol) or distillation (3-undecanol).

decreased bulk of the amino acid residues (L-Ala) on the catalyst caused a decrease in selectivity for both aromatic and aliphatic aldehydes (rxn 9 and 10). With increased steric demand (L-Val), enhanced stereoselection was observed with benzaldehyde (rxn 11). In contrast, the aliphatic aldehydes showed diminished enantioselectivity and reduced yields (rxn 12 and 13).

Optimization of a catalyst for particular applications will be facilitated by the use of solid-phase variants, which will permit simultaneous reactions to be run in parallel.[11] Preliminary results with the "Wang-supported L-Phe-L-Phe catalyst" **5** are shown in Table 4.[12] The Et_2Zn-activated resin

Table 4. Solid-Phase Ligand Functions As Catalyst with Only Slightly Reduced Enantioselectivities





rxn	temperature	chemical yield	enantiomeric excess
14	RT	98%	64%
15	RT	98%	68%
16a	RT (18 hrs)	73%	–
16b	30°C (+ 5 hrs)	82%	75%
16c	40°C (+24 h)	89%	79%

was then used multiple times without degradation of either the yields or the enantioselectivities (rxn 14 and 15).[13] Overall, the yields were only slightly diminished relative to the solution-phase catalyst, and the ee's were lower. Since the ee seemed to increase upon reuse of the catalyst (rxn 15), it was assumed that Et_2Zn removed impurities that affected the enantioselection. Thus, for the next reaction (rxn 16) the L-Phe-L-Phe-bearing resin was "washed" with excess Et_2Zn prior to use. The conversion was monitored by GC as a function of time and temperature (rxn 16a−c). As expected,

(10) (a) Lutz, C.; Jones, P.; Knochel, P. *Synthesis* **1999**, *2*, 312. (b) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895. (c) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1609.

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(12) The L-Phe-L-Phe Schiff Base ligand has been synthesized using both the Merrifield and Wang resins: (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149. (b) Lu, G.; Mojsov, S.; Tam, J. P.; Merrifield, R. B. *J. Org. Chem.* **1981**, *46*, 3433. (c) Wang, S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

(13) (a) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (b) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712. (c) Wantanabe, M.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 837. (d) Soai, K.; Wantanabe, M.; Yamamoto, A. *J. Org. Chem.* **1990**, *55*, 4140. (e) Itsuno, S.; Frechèt, J. M. *J. Org. Chem.* **1987**, *52*, 4140.

the rate of product formation increased with increasing time and temperature. Surprisingly, the ee's were enhanced as well. The explanation for this behavior may involve increased swelling of the polymer at higher temperatures, "uncoiling" of the polystyrene backbone, or other effects.[14]

Assuming that two zinc atoms are involved in alkyl transfer, the inner zinc is surrounded by electron-donating nitrogens, while the outer zinc is only solvated by exchangeable oxygens.[15] Given the observed results, the mechanism may be related to the "ate" or "ate-like" mechanism proposed by Kitamura[16] or may involve reversed roles for the two zinc atoms, with the "inner zinc" functioning as a chiral Lewis acid[17] and the "outer zinc" functioning as the alkyl donor (Figure 1). The role of the THF is not clear. It may be required in order to effect alkyl transfer from Et_2Zn to the "inner zinc" (Soai mechanism) or may simply prevent aggregation. Obviously, further study will be required for a complete understanding of this new catalyst system.

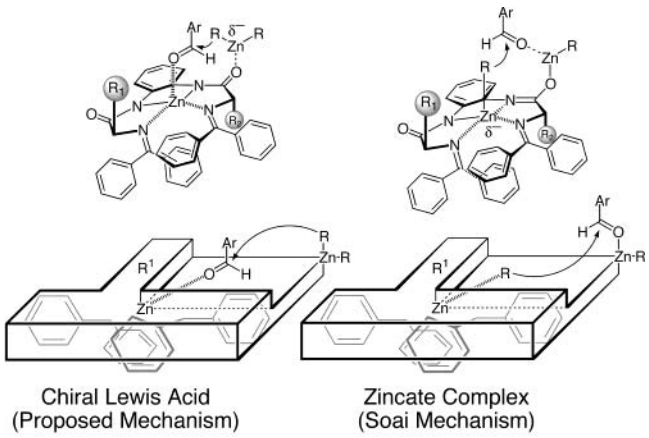

Figure 1. Possible mechanisms for the observed facial enantioselectivity.

Acknowledgment. We thank the U.S. Army (DAMD 17-99-1-9539) and the Arizona Disease Control Research Commission for the support of this work and Prof. Michael Doyle for use of his capillary GC.

Supporting Information Available: Complete experimental procedures, spectral characterization of the ligands and intermediates (^{1}H NMR, ^{13}C NMR, and IR), GC traces, and column conditions used. This material is available free of charge via the Internet at http://pubs.acs.org.

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